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FILE 'USPAT' ENTERED AT 13:15:26 ON 16 MAR 1999

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=> s B7/clm and tumor?/clm

          167 B7/CLM
         3593 TUMOR?/CLM
L1          6 B7/CLM AND TUMOR?/CLM

=> t l1 1-6


1.  5,861,310, Jan. 19, 1999, Tumor cells modified to express B7-2 with
increased immunogenicity and uses therefor; Gordon J. Freeman, et al.,
435/325; 424/93.2, 277.1; 435/375 [IMAGE AVAILABLE]

2.  5,858,776, Jan. 12, 1999, Tumor cells with increased immunogenicity
and uses therefor; Suzanne Ostrand-Rosenberg, et al., 435/325; 424/93.21;
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in ruminants; John F. T. Griffin, 435/4, 7.24, 7.92, 13, 29; 436/501
[IMAGE AVAILABLE]

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in tissue; Paul F. Turner, 607/154; 219/696, 704 [IMAGE AVAILABLE]

=> t 1-2 fro clm


US PAT NO:      5,861,310 [IMAGE AVAILABLE]              L1: 1 of 6
DATE ISSUED:    Jan. 19, 1999
TITLE:          Tumor cells modified to express B7-2 with increased
                  immunogenicity and uses therefor
INVENTOR:       Gordon J. Freeman, Brookline, MA
                Lee M. Nadler, Newton, MA
                Gary S. Gray, Brookline, MA
ASSIGNEE:       Dana-Farber Cancer Institute, Boston, MA (U.S. corp.)
APPL-NO:        08/456,104
DATE FILED:     May 30, 1995
REL-US-DATA:    Continuation-in-part of Ser. No. 147,773, Nov. 3, 1993,
                  abandoned.
INT-CL:         [6] C12N 5/00; C12N 5/10; C12N 5/08
US-CL-ISSUED:   435/325, 375; 424/277.1, 93.2
US-CL-CURRENT:  435/325; 424/93.2, 277.1; 435/375
SEARCH-FLD:     435/172.3, 240.2, 375, 325; 424/277.1, 93.2
REF-CITED:
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ART-UNIT: 162
PRIM-EXMR: Jasemine C. Chambers
ASST-EXMR: Karen M. Hauda
LEGAL-REP: Amy E. Mandragouras, Megan E. Williams

ABSTRACT:
Tumor cells modified to express a T cell costimulatory molecule are disclosed. In one embodiment, the costimulatory molecule is a CD28/CTLA4 ligand, preferably a B lymphocyte antigen B7. The tumor cells of the invention can be modified by transfection with nucleic acid encoding a T cell costimulatory molecule, by using an agent which induces or increases expression of a T cell costimulatory molecule on the tumor cell surface or by coupling a T cell costimulatory molecule to the tumor cell surface. Tumor cells further modified to express MHC class I and/or class II molecules or in which expression of an MHC associated protein, the invariant chain, is inhibited are also disclosed. The modified tumor cells of the invention can be used in methods for treating a patient with a tumor, preventing or inhibiting metastatic spread of a tumor or preventing or inhibiting recurrence of a tumor. A method for specifically inducing a CD4.sup.+ T cell response against a tumor and a method for treating a tumor by modification of tumor cells in vivo are disclosed.
18 Claims, 8 Drawing Figures

US PAT NO: 5,858,776 [IMAGE AVAILABLE] L1: 2 of 6

CLAIMS:

CLMS(1)

We claim:

1. An isolated mammalian **tumor** cell transfected withan exogenous nucleic acid molecule encoding a mammalian **B7** molecule, wherein said molecule is expressed by said **tumor** cell and wherein said **B7** molecule has the ability to costimulate a T cell and the ability to bind

CD28 or CTLA4 ligand.

CLMS(2)

2. The **tumor** cell of claim 1 which expresses an MHC class II molecule.

CLMS(3)

3. The **tumor** cell of claim 1 which expresses an MHC class I molecule.

CLMS(4)

4. The **tumor** cell of claim 1 which normally expresses an MHC class II associated protein, the invariant chain, and wherein expression of the invariant chain is inhibited.

CLMS(5)

5. The **tumor** cell of claim 1 wherein the exogenous nucleic acid is a cDNA in a recombinant expression vector.

CLMS(6)

6. The **tumor** cell of claim 5 further transfected with at least one exogenous nucleic acid molecule encoding:
(a) at least one MHC class II .alpha. chain protein, and
(b) at least one MHC class II chain protein,
wherein said MHC class II .alpha. chain protein(s) and said MHC class II .beta. chain protein(s) is expressed by said **tumor** cell.

CLMS(7)

7. The **tumor** cell of claim 6 which does not express MHC class II molecules prior to transfection of the exogenous nucleic acid molecule encoding said MHC class II .alpha. chain protein(s) and said MHC class II .beta. chain protein(s) into the **tumor** cell.

CLMS(8)

8. The **tumor** cell of claim 1 further transfected with at least one nucleic acid molecule encoding at least one MHC class I .alpha. chain protein wherein said MHC class I protein(s) is expressed by the **tumor** cell.

CLMS(9)

9. The **tumor** cell of claim 8 further transfected with an exogenous nucleic acid molecule encoding a .beta.-2 microglobulin protein, wherein said .beta.2 microglobulin protein is expressed by the **tumor** cell.

CLMS(10)

10. The rumor cell of claim 4 wherein expression of the invariant chain is inhibited by transfection of the **tumor** cell with a nucleic acid which is antisense to a regulatory or a coding region of the invariant chain gene.

CLMS(11)

11. The **tumor** cell of claim 1 which is a sarcoma.

CLMS(12)

12. The **tumor** cell of claim 1 which is a lymphoma.

CLMS(13)

13. The **tumor** cell of claim 1 which is selected from a group consisting of a melanoma, a neuroblastoma, a leukemia and a carcinoma.

CLMS(14)

14. An isolated mammalian sarcoma cell transfected with an exogenous nucleic acid molecule encoding a mammalian **B7** molecule wherein said **B7** molecule is expressed in said **tumor** cell and wherein said **B7** molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand.

CLMS(15)

15. The sarcoma cell of claim 14 which expresses an MHC class II molecule.

CLMS(16)

16. The sarcoma cell of claim 15 which expresses an MHC class I molecule.

CLMS(17)

17. The **tumor** cell as in any one of claims 1, 2, 5, 13, or 14 wherein the cell is further transfected with an exogenous nucleic acid molecule encoding a cytokine, wherein said cytokine is expressed in said **tumor** cell.

CLMS(18)

18. A composition comprising an amount of the **tumor** cells of any of claims 1, 2, 5, 6, 12, 13, or

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=> s cd28/clm or cd(w)28/clm

           25 CD28/CLM
        49412 CD
       149107 28/CLM
            1 CD(W)28/CLM
L2         26 CD28/CLM OR CD(W)28/CLM

=> s l2 and tumor?

        26324 TUMOR?
L3         24 L2 AND TUMOR?

=> s l3 and tumor?/clm

         3593 TUMOR?/CLM
L4          6 L3 AND TUMOR?/CLM

=> t 14 1-6
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1. 5,863,538, Jan. 26, 1999, Compositions for targeting the vasculature of solid **tumors**; Philip E. Thorpe, et al., 424/136.1, 138.1, 141.1, 154.1, 155.1, 172.1, 173.1, 174.1, 181.1; 530/387.3, 387.7, 388.22 [IMAGE AVAILABLE]

2. 5,861,310, Jan. 19, 1999, **Tumor** cells modified to express B7-2 with increased immunogenicity and uses therefor; Gordon J. Freeman, et al., 435/325; 424/93.2, 277.1; 435/375 [IMAGE AVAILABLE]

3. 5,858,776, Jan. 12, 1999, **Tumor** cells with increased immunogenicity and uses therefor; Suzanne Ostrand-Rosenberg, et al., 435/325; 424/93.21; 435/69.1, 320.1, 354, 366, 375 [IMAGE AVAILABLE]

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5. 5,750,105, May 12, 1998, Recombinant antibodies for human therapy; Roland A. Newman, et al., 424/133.1, 137.1, 138.1, 177.1; 530/387.3 [IMAGE AVAILABLE]

6. 5,712,149, Jan. 27, 1998, Chimeric receptor molecules for delivery of co-stimulatory signals; Margo R. Roberts, 435/252.3, 69.7, 320.1; 530/350; 536/23.4 [IMAGE AVAILABLE]

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SESSION WILL BE HELD FOR 30 MINUTES
U.S. Patent & Trademark Office SESSION SUSPENDED AT 13:19:45 ON 16 MAR 199

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Fearon, E., et al., "Interleukin-2 Production by Tumor Cells Bypasses T Helper Function in the Generation of an Antitumor Response," Cell, vol. 60, 397-403 (1990).
Freedman, A., et al., "B7, a B Cell-Restricted Antigen that Identifies Preactivated B Cells," J. Immunology, vol. 139, 3260-3267 (1987).
Schultz, K., et al., "The Role of B Cells for in Vivo T Cell Responses to a Friend Virus-Induced Leukemia," Science, vol. 249, 921-923 (1990).
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ART-UNIT: 162
PRIM-EXMR: Jasemine C. Chambers
ASST-EXMR: Karen M. Hauda
LEGAL-REP: Amy E. Mandragouras, Megan E. Williams

ABSTRACT:
Tumor cells modified to express one or more T cell costimulatory molecules are disclosed. Preferred costimulatory molecules are B7-2 and B7-3. The tumor cells of the invention can be modified by transfection with nucleic acid encoding B7-2 and/or B7-3, by using an agent which induces or increases expression of B7-2 and/or B7-3 on the tumor cell or by coupling B7-2 and/or B7-3 to the tumor cell. Tumor cells modified to express B7-2 and/or B7-3 can be further modified to express B7. Tumor cells further modified to express MHC class I and/or class II molecules or in which expression of an MHC associated protein, the invariant chain, is inhibited are also disclosed. The modified tumor cells of the invention can be used in methods for treating a patient with a tumor, preventing or inhibiting metastatic spread of a tumor or preventing or inhibiting recurrence of a tumor. A method for specifically inducing a CD4.sup.+ T cell response against a tumor and a method for treating a tumor by modification of tumor cells in vivo are disclosed.
10 Claims, 9 Drawing Figures

US PAT NO: 5,861,310 [IMAGE AVAILABLE] L1: 1 of 6

CLAIMS:

CLMS(1)

We claim:

1. An isolated mammalian **tumor** cell transfected with an exogenous nucleic acid molecule encoding a mammalian B7-2 molecule, wherein said B7-2 molecule is expressed in said **tumor** cell and wherein said B7-2

molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand.

CLMS(2)

2. The **tumor** cell of claim 1, wherein the exogenous nucleic acid is a cDNA in a recombinant expression vector.

CLMS(3)

3. The **tumor** cell of claim 1, which is a sarcoma.

CLMS(4)

4. The **tumor** cell of claim 1, which is a lymphoma.

CLMS(5)

5. The **tumor** cell of claim 1, which is selected from a group consisting of a melanoma, a neuroblastomas, a leukemia and a carcinoma.

CLMS(6)

6. An isolated mammalian sarcoma cell transfected with an exogenous nucleic acid molecule encoding a mammalian B7-2 molecule, wherein said B7-2 molecule is expressed in said **tumor** cell and wherein said **B7** molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand.

CLMS(7)

7. A composition comprising an amount of the rumor cells of claim 1 and a physiologically acceptable carrier.

CLMS(8)

8. A composition comprising an amount of the **tumor** cells of claim 6, and a physiologically acceptable carrier.

CLMS(9)

9. The cell of any of claims 1, 2, 3, 4, 5, or 6, wherein the nucleic acid molecule has the nucleotide sequence shown in SEQ ID NO: 1.

CLMS(10)

10. The cell of any of claims 1, 2, 3, 4, 5, or 6, wherein the B7-2 molecule has the amino acid sequence shown in SEQ ID NO: 2.

US PAT NO: 5,858,776 [IMAGE AVAILABLE] L1: 2 of 6
DATE ISSUED: Jan. 12, 1999
TITLE: Tumor cells with increased immunogenicity and uses therefor
INVENTOR: Suzanne Ostrand-Rosenberg, Columbia, MD
Sivasubramanian Baskar, Ellicott City, MD
Laurie H. Glimcher, West Newton, MA
Gordon J. Freeman, Brookline, MA
Lee M. Nadler, Newton, MA
ASSIGNEE: Repligen Corporation, Boston, MA (U.S. corp.)
Dana-Farber Cancer Institute, Boston, MA (U.S. corp.)
President and Fellows of Harvard College, Cambridge, MA (U.S. corp.)
APPL-NO: 08/147,772
DATE FILED: Nov. 3, 1993
INT-CL: [6] C12N 15/09; C12N 5/10; C12N 15/63

US-CL-ISSUED: 435/325, 69.1, 172.3, 320.1, 375, 354, 366
US-CL-CURRENT: 435/325; 424/93.21; 435/69.1, 320.1, 354, 366, 375
SEARCH-FLD: 435/172.3, 69.1, 375, 320.1, 325, 354, 366
REF-CITED:

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Harding, F.A. et al. (1993) "CD28-B7 Interactions Allow the Induction of CD8.sup.+ Cytotoxic T Lymphocytes in the Absence of Exogenous Help" J. Exp. Med. 177:1791-1796.
Baskar, S. et al. (1993) "Constitutive Expression of B7 Restores Immunogenicity of Tumor Cells Expressing Truncated Major Histocompatibility Complex Class II Molecules" Proc. Natl. Acad. Sci. USA 90:5687-5690.
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